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Pharmacokinetic-Pharmacodynamic Modeling in the Data Analysis and Interpretation of Drug-induced QT/QTc Prolongation

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ABSTRACT

In this review, factors affecting the QT interval and the methods that are currently in use in the analysis of drug effects on the QT interval duration are overviewed with the emphasis on (population) pharmacokinetic-pharmacodynamic (PK-PD) modeling. Among which the heart rate (HR) and the circadian rhythm are most important since they may interfere with the drug effect and need to be taken into account in the data analysis. The HR effect or the RR interval (the distance between 2 consecutive R peaks) effect is commonly eliminated before any further analysis, and many formulae have been suggested to correct QT intervals for changes in RR intervals. The most often used are Bazett and Fridericia formulae introduced in 1920. They are both based on the power function and differ in the exponent parameter. However, both assume the same exponent for different individuals. More recent findings do not confirm this assumption, and individualized correction is necessary to avoid under- or overcorrection that may lead to artificial observations of drug-induced QT interval prolongation. Despite the fact that circadian rhythm in QT and QTc intervals is a well-documented phenomenon, it is usually overlooked when drug effects are evaluated. This may result in a false-positive outcome of the analysis as the QTc peak due to the circadian rhythm may coincide with the peak of the drug plasma concentration. In view of these effects interfering with a potential drug effect on the QTc interval and having in mind low precision of QT interval measurements, a preferable way to evaluate the drug effect is to apply a population PK-PD modeling. In the literature, however, there are only a few publications in which population PK-PD modeling is applied to QT interval prolongation data, and they all refer to antiarrhythmic agents. In this review, after the most important sources of variability are outlined, a comprehensive population PK-PD model is presented that incorporates an individualized QT interval correction, a circadian rhythm in the individually corrected QT intervals, and a drug effect. The model application is illustrated using real data obtained with 2 compounds differing in their QT interval prolongation potential. The usefulness of combining data of several studies is stressed. Finally, the standard approach based on the raw observations and formal statistics, as described in the Preliminary Concept paper of the International Conference on Harmonization, is briefly compared with the method based on population PK-PD modeling, and the advantages of the latter are outlined.

KEYWORDS: cardiovascular safety of drugs, QT/QTc prolongation caused by drugs, concentration-response relationship, pharmacokinetic-pharmacodynamic modeling

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INTRODUCTION

Since the mid 1980s, evidence has accumulated that several classes of noncardiac drugs significantly prolong the QT interval of the surface electrocardiogram (ECG) and have cardiotoxic potential (risk of life-threatening arrhythmias).[1,2] Drug-induced lengthening of the QT interval (stemming from a drug's ability to prolong the cardiac action potential duration) has been associated with the occurrence of ventricular tachyarrhythmias, namely, torsades de pointes (TdP), a polymorphous ventricular arrhythmia that may cause syncope and degenerate into ventricular fibrillation.[3] Although there is an ongoing debate in the literature on the clinical significance of a prolonged QT interval,[4,5] it has been found to be a risk factor for sudden death due to cardiac arrest[6] and also for all-cause mortality.[7,8]

Several interventions by regulatory agencies and/or drug companies have fostered the discussion on the impact of QT-prolonging effects on drug development.[9] While the degree of QT interval prolongation is recognized as an imperfect biomarker for the proarrhythmic risk, there is at least a qualitative relationship between QT interval prolongation and the risk of TdP. Cardiac safety considerations need therefore to be an integral part of phase 1 and 2 studies of every investigational drug. Once proarrhythmic safety of a new drug has been established in early development, large phase 3 studies and postmarketing surveillance can be limited to less strict designs and less laborious investigations (eg, a smaller number of ECGs involved in patient monitoring, less precise approaches to heart rate correction).[2]

According to the current practice (at least in some pharmaceutical companies), every compound that enters clinical development receives an electrocardiographic evaluation that typically includes at least one study dedicated to assessing its effect on cardiac repolarization (thorough QT/QTc study[9]). Given that routine, the question of proper estimation of QT prolongation caused by drugs from clinical study data and correct interpretation becomes a crucial one. This question is firmly related to the problem of study design. Due to high inter- and intra-individual variability of QT intervals there is a substantial risk of false-positive or false-negative study outcomes if the analysis of results is performed without taking into account all of the inherent complexities of the data.

The aim of this review is to give an overview of factors affecting the QT interval and also of the methods that are currently in use in the analysis of drug effects on the QT interval duration with the emphasis on pharmacokinetic-pharmacodynamic (PK-PD) modeling.

Variability in the QT Interval Duration

Figure 1 shows the intervals typically measured on an ECG. The normal QT interval is from the beginning of the QRS complex to the end of the T-wave. It represents the time between the onset of electrical depolarization of the ventricles and the end of repolarization, that is, it reflects the duration of individual action potentials in the cardiac myocytes. The QT interval obviously shortens with increasing heart rate (HR) or reducing the RR interval, and this is one of the major sources of QT variability. The QT interval corrected for changes in the RR interval is generally notated QTc (without specifying the details of correction). Other subject-related factors potentially affecting the QT or QTc interval[2] are listed below:

1. Genetic (long QT syndrome)
2. Food intake
3. Circadian rhythm
4. Sex
5. Obesity
6. Physical activity
7. Electrolyte disturbances
8. Blood glucose level
9. Blood pressure
10. Alcoholism
11. Age
12. Presence of a U-wave

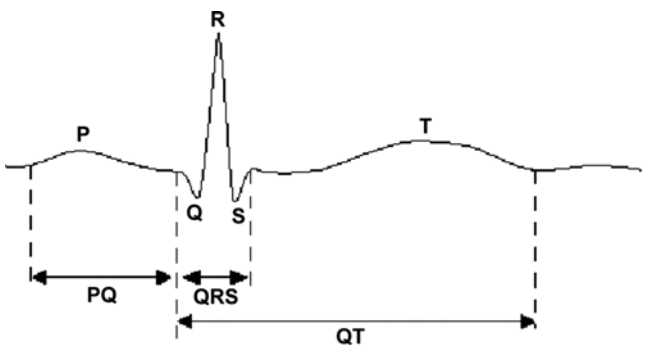

Figure 1. Schematic ECG trace showing the QT interval and R peak.

The effect of food intake is quite substantial. Increases of 16 to 23 milliseconds have been reported during the 60 minutes following a meal.[10] Furthermore, on average QTc interval is longer in females by ~8 to 10 milliseconds than in males.[11,12] Also, females have higher incidence of TdP than men.[13] Obesity is often associated with QTc prolongation and a 10 kg increase in fat mass has been linked to a >5 millisecond increase in QTc.[14,15]

The QT interval adapts to the changes in HR rather slowly (90% of the adaptation requires ~2 minutes), and this causes the phenomenon known as QT/RR hysteresis.[16,17] It is important therefore to ensure that no ECGs are recorded when the heart rate is rising or falling. Specifically, if ECGs are recorded while the heart rate is increasing, and the QT interval is not adapted to the faster heart rate, an artificially prolonged QTc interval will result because of the mismatch between the RR and QT intervals.

Difficulty in identifying the end of the T-wave can introduce further variability in the measurement of the QT interval resulting in low precision.[18] Also, manual and automatic measurements may not correlate well.[19] Morphological abnormalities of the T-wave, noise in the signal as well as confusion between the T- and U-wave may easily invalidate automatic measurements. For this reason, no automatic algorithm can be suggested as sufficiently precise and robust to satisfy the precision required in the assessment of drug cardiac safety. Although some combinations of manual and automatic measurements are permissible when subjected to advanced quality control, it is safer to use manual measurements taken by experienced personnel.[2] These factors have the potential to introduce inconsistencies within and across studies. By contrast, the RR interval is measured with high precision as the R peak on the ECG can be easily positioned (Figure 1).

Taking into account multiple sources of variability in QT intervals differentiating the drug effect is not easy; this requires adequate data analysis methods. PK-PD modeling in general and population modeling in particular[20,21] provides validated tools to split the overall variability into components and estimate them with sufficient precision.

QT-RR Relationship

Appropriate correction of QT intervals for changes in RR intervals or HR is an essential element of the evaluation of drug-induced QT prolongation. Since 1920 when 2 pioneering

articles appeared[22,23] a lot of attention has been paid to finding a "magic" formula that provides the ideal correction such that the corrected QT interval is independent of the RR interval (see Malik and Camm for a review[2]). In spite of the common understanding that such a formula does not exist, most of the authors working in the area of cardiovascular drug safety still use Bazett correction as shown in Equation1:

$$QTcB = \frac{QT}{\sqrt{RR}} = QT \times RR^{-0.5}, \quad (1)$$

where RR is in seconds; or the Fridericia correction formula as shown in Equation 2:

$$QTcF = \frac{QT}{\sqrt[3]{RR}} = QT \times RR^{-0.333} \quad (2)$$

More recently, a linear formula has appeared[24] (QT in seconds) as shown in Equation 3:

$$QTcL = QT + 0.154 \times (1 - RR) \quad (3)$$

Figure 2 compares the 3 formulas using as an example a pooled data set comprising QT-RR measurements obtained before treatment in 70 healthy individuals from 4 cardiovascular safety studies. This data set will be used throughout the current review to illustrate various aspects of the QT interval prolongation modeling. Among the 3 formulas, that of Fridericia performs on average quite well; the smoother (loess smooth) is almost horizontal. By contrast, in case of Bazett and linear correction, the loess smoothers are inclined. However, the major problem with these (and other) formulas is that they assume the same correction for every individual, which contradicts with reality; individuals show different QT-RR relationships.[2,25,26]

An obvious solution to this problem is to use an individualized correction. A correction equation is to be fitted to individual pretherapy QT-RR interval data over a range of heart rates, then individual estimates of parameter(s) of the equation are used to correct on-treatment QT values. Apparently, the first application of this method was in the article by Galeazzi et al[27] in which a linear correction model was fitted to individual pretreatment data. The authors mentioned

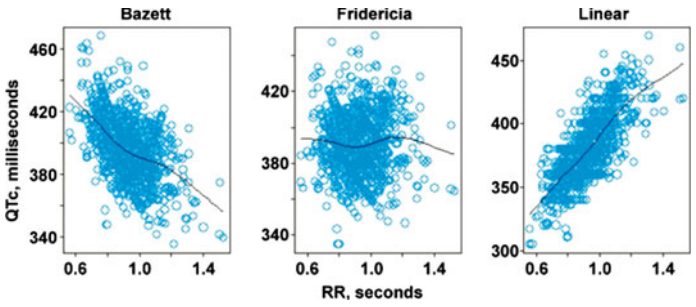

Figure 2. Comparison of the correction formulas using placebo data of 4 cardiovascular safety studies. All individual measurements are pooled together. Smoothing lines are drawn through the data points.

the inaccuracy of the Bazett correction that magnifies drug- and heart rate-related effects. The same approach was used by Bryson et al[28] and Whiting et al.[29] Since that time, individual correction has not often been used. Only recently it has been reintroduced (Malik and Camm,[2] Malik,[18] and Desai et al[30]). The power correction model resembling Equation 1 or 2 is recommended as shown in Equation 4:

$$QT = QT_c \times RR^{\alpha} \quad (4)$$

However, by contrast to the Bazett or Fridericia correction methods, the exponent α is allowed to vary across individuals. The approach based on the individualized correction has been acknowledged by the International Conference on Harmonization (ICH) Preliminary Concept Paper.[9] At present, however, this approach is still not used broadly since collecting sufficiently large numbers of pretreatment QT interval measurements in each subject needed to estimate individual α with precision is cumbersome.

Mixed-effects modeling provides a practical solution to the problem of individualized QT correction. Taking the model represented by Equation 4, a j-th measured QT interval in an i-th individual, QT_{ij}, can be expressed as follows[31]:

$$QT_{ij} = QTc_i \cdot RR_{ij} \cdot (1 + \varepsilon_{ij}) \quad (5)$$

QTc_I denotes a corrected QT interval in an i-th individual, α_i is a subject-specific exponent, and ϵ_{ij} is a residual normal error. Fitting Equation 5 to the above-mentioned pretreatment data in 70 healthy subjects enables the estimation (through the Bayesian posterior procedure) of individual QTc_I, which is a baseline value within a study day, and α_i. Figure 3 illustrates the quality of correction achieved by applying mixed-effects modeling as implemented in NONMEM software (GloboMaX, Ellicott City, MD).[32] First-order conditional estimation (FOCE) method with correction for η-ϵ interaction was used. In this figure, QT measurements obtained before treatment in randomly selected individuals were corrected using the formula shown in Equation 6:

$$QTcl_{ij} = \frac{QT_{ij}}{RR_{ij}^{\alpha_i}} \quad (6)$$

and plotted against RR. We will distinguish QTc_I, which is a parameter of Equation 5 and those that will follow, and QTc_I, which are QT interval measurements individually corrected using Equation 6. From Figure 3, between individual variability (BIV) in α is evident, and applying the mixed-effects technique gives an adequate QT correction even with a relatively small number of measurements per individual per study day (10–15), which is typical for cardiovascular safety studies.

A recent publication by Li et al[33] also suggests mixed-effects modeling instead of the individual regression. The authors also used the power model, Equation 4, and applied log-transformation to make it linear.

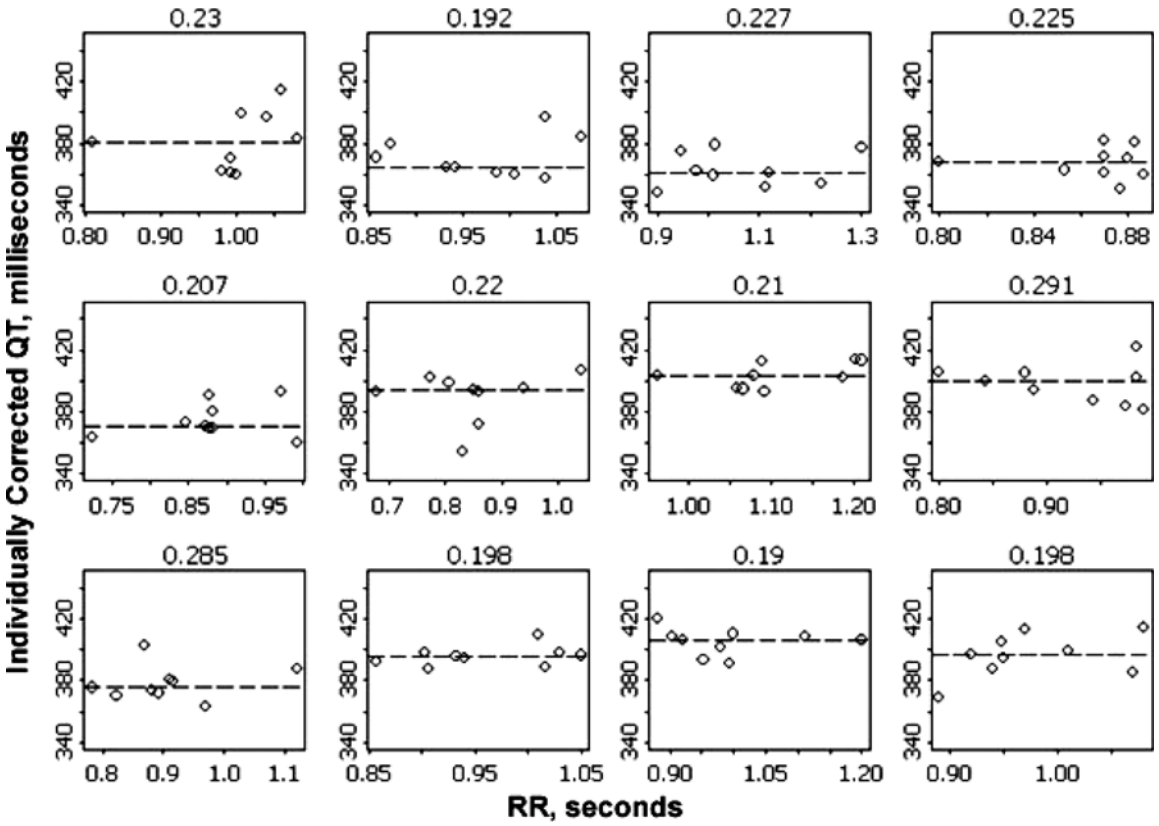

Figure 3. Individual QT correction based on population modeling. Panel titles are Bayes empirical estimates of the exponent α.

One should stress that an adequate QT correction is a prerequisite for unbiased estimation of drug effects. As shown in Malik[34] and Malik et al,[35] the imprecision in HR correction may lead to artificial observations of drug-induced QT interval changes.

Pharmacokinetic-Pharmacodynamic Modeling of QT Prolongation

In this section, as well as throughout the whole review only a little attention will be paid to PK aspects of data analysis. The emphasis will be on PD modeling, particularly, on how the drug effect is implemented and statistically evaluated. For brevity, only clinical data modeling will be overviewed; analyses of animal data[36-41] will not be included.

There are not many publications in the literature in which PK-PD modeling of drug effects on the QT interval was performed. Furthermore, most (if not all) of them consider antiarrhythmic drugs for which the QT interval prolongation is a target pharmacological action. Probably the first publication presenting a form of PK-PD analysis was that by Galeazzi et al[27] who studied the effect of procainamide on the QT interval. The authors did not use any specific PD model, but rather developed a PK model for plasma and saliva concentrations during and after intravenous infusion and demonstrated that the corrected QT interval change from a pretreatment value shows hysteresis when plotted against plasma concentration. The hysteresis collapsed after plotting the PD data vs the saliva concentration. Saliva thus played a role of an effect compartment. As one can judge from the graphical presentation the overall shape of the concentration-effect profiles resembled a sigmoid Emax curve; however, PD modeling was not attempted.

Early PK-PD modeling of the concentration-effect relationship was based on individual model fitting (eg, various formulations of disopyramide were studied[28,29]). QT intervals were individually corrected by fitting the linear model of the following form to pretreatment data (authors' notations are used)[29]:

$$QT_p = b + m \cdot HR \qquad (7)$$

where QT_p is the predicted QT interval, b is the intercept on the QT axis, m is the slope of the linear regression, and HR is the mean heart rate determined from the measurements of 20 consecutive cardiac cycles.

Whiting et al[29] developed a PK-PD model using, as the dependent variable, absolute change of the corrected QT interval from baseline. The model included an effect compartment linking the plasma concentration to the pharmacodynamic effect. The selected PD submodel was a linear one:

$$E = mCe + i \qquad (8)$$

where E is a drug effect, C_e is a model-predicted effect compartment concentration, and m and i are slope and intercept

parameters, respectively. There were several versions of PK models tested, and they were fitted to each individual data set separately. On the contrary, no PD models alternative to the linear one were compared. In a later PK-PD study of disopyramide effect on QTc,[42] the linear PD model was also used, and it was shown that the unbound drug concentration better predicted the response as compared with the total concentration. The equilibration half-life for the effect compartment was ~1.6 minutes.

A linear model similar to that of Equation 8 was used by Holford et al[43] in their study of quinidine effects on QT intervals and other cardiovascular parameters after intravenous and oral administration. QT correction for RR was performed as in Whiting et al[29] using a linear relationship (Equation 7). The intercept parameter of the PD model (Equation 8) was effectively negligible, and the slope parameter differed for the 2 administration routes. The authors believed that the apparent change in the sensitivity to quinidine after an oral dose when compared with an intravenous dose was attributable to one or more active metabolites that were present in higher concentrations at oral administration because of the first-pass metabolism of the drug. The authors mentioned that QTc after placebo administration did not remain constant throughout the day, which may be a consequence of a circadian rhythm (see below). However, no attempt to model circadian variability was made.

Piergies et al[44] investigated PK-PD relationships in QT effects of N-acetylprocainamide infused intravenously to 5 patients with arrhythmias. This was a single-dose study, and the PK-PD model included an effect compartment. The model was fitted to each individual's data separately, and an obvious BIV was seen: in 4 patients the linear model was adequate, whereas in one patient the Emax model was needed, although no formal model selection was performed. Apparently, the patient with a saturable concentration-response profile differed from others with respect to sensitivity; lower drug concentrations were needed to achieve the maximum response. An advantage of the analysis was the inclusion of baseline QTc in the model; it was estimated together with other PD model parameters. However, a serious drawback was the use of the Bazett correction formula.

The Emax model was fitted to the mean QTc changes from baseline vs plasma concentrations of disopyramide enantiomers.[45] The linear correction formula was used to derive QTc intervals in 5 healthy subjects; however no individualization was applied. Unbound plasma concentrations of enantiomers were obtained through individual PK modeling and averaged.

In a more recent study of quinidine effects upon intravenous infusion,[46] the linear and sigmoid Emax models were compared, and the latter did not provide better fit when applied to QTc data. A serious disadvantage of this study was the use of the Bazett correction to obtain QTc values.

(+)-Sotalol effects on QTc intervals in healthy male subjects were analyzed in the work by Uematsu et al.[47] The authors did not report the correction method used. The drug was administered orally and intravenously, and in the latter case PK-PD modeling was attempted. The model included an effect compartment (the equilibration half-life was ~0.6 hours) and was linear with respect to the effect-compartment concentration impact on QTc intervals.

Shi et al developed PK and PK-PD models for sematilide effects on QTc intervals.[48] The latter were derived using a linear correction formula similar to Equation 3 without using individualization that downgrades the validity of the analysis results. On the other hand, by contrast to many other investigators, no baseline subtraction prior to modeling was made and the baseline QTc interval was estimated as one of the PD model parameters. Six healthy individuals were assessed, and 3 PD models were compared: a linear one, an E-max model, and a sigmoid Emax model. The model included also an effect compartment to account for a delay in the QTc response. Individual model fitting was performed using NONMEM software, and it turned out that in 4 individuals the linear model was quite adequate whereas in the remaining 2 subjects, an Emax model was superior. This may be a manifestation of BIV in the maximum effect parameter (E_{max}). In subjects with higher E_{max} it could not be estimated, and the linear model was appropriate.

Results of PK-PD modeling of QTc interval prolongation after intravenous infusion of dofetilide (0.5 mg over 30 minutes) were reported by Le Coz et al.[49] QT measurements were corrected by using Fridericia formula, and the linear and sigmoid Emax PD models were compared. An equilibration rate constant for the effect compartment was estimated together with the PD parameters after fitting the model to the individual data of 10 male subjects. In only 2 of them the linear PD model was sufficient, and in the remaining subjects all parameters of the sigmoid Emax model were estimated with a good precision. The estimated baseline QTcF was 368 ± 11 milliseconds (mean ± SD), the maximum increase was 131 ± 57 milliseconds, and the half-maximum concentration was 2.2 ± 0.6 ng/mL. The Hill parameter varied substantially between individuals: the range was 1.2 to 6.0 with the mean equal to 2.9 ± 1.8. This study was the first one in which the sigmoid Emax model was used and successfully fitted to the data of several individuals providing information on drug activity and potency. An obvious disadvantage of the study was the nonindividualized QT correction.

QTcB intervals in pediatric patients with supraventricular and ventricular tachyarrhythmia were analysed against

steady-state plasma concentrations of a β-blocker sotalol.[50] A linear relationship was observed, and this finding was further explored in a population PK-PD study.[51] Two PD models were compared:

$$E = E_0 + SL \cdot C \tag{9}$$

$$E = E_0 + E_{\max} \cdot \frac{C}{EC_{50} + C} \tag{10}$$

where E_0 is the average baseline effect, and C is the drug plasma concentration. The PK model was the 2-compartment with intravenous administration and was developed before simultaneous PK-PD analysis. Final estimates of the PK parameters were obtained simultaneously with the PD parameters. BIV in parameters was modeled using a lognormal distribution. Three models for the residual error in concentrations and QTcB were compared. Finally, the combined additive+proportional error was selected for the PK model and the additive error for the PD model. The comparison of the linear and the Emax PD models (Equation 9 and 10, respectively) did not show any preference of the latter, and the linear one was finally selected. Patient sex affected E_0 (it was 17.3 milliseconds higher in females than in males); however, the difference was not significant according to the preselected criterion: objective function decrease by more than 10.8 ($P < .001$, $df = 1$). Other patient characteristics, age in particular, did not influence PD parameters. For a typical pediatric patient, the final PD model for QTcB prolongation caused by sotalol was as follows:

$$QTcB = 405 + 0.0162 \cdot C \tag{11}$$

The precision of parameter estimates was high (coefficient of variation [CV] of 1% and 15% for E_0 and SL, respectively); however, the residual error SD was 19.1 milliseconds, which means high uncertainty about the baseline QTcB (95% prediction interval was 367–443 milliseconds). The residual error might be overestimated because of the Bazett correction used. Also, an important process inherent to QT and QTc intervals was ignored: a circadian rhythm.

Population PK-PD modeling of azimilide effects on QTc interval in cardiac patients was reported by Phillips et al.[52] The authors did not mention the correction method they used; however, from the other publications on azimilide from the same company,[53,54] it may be assumed that it was the Bazett formula (Equation 1). The data of 3 clinical studies were combined for the analysis. The independent variable was the observed azimilide concentration at the time of the QTc measurement, so there was no PK submodel in the PK-PD model. With regard to the PD model, in addition to the linear and Emax models, the sigmoid Emax model was tested. Finally, the Emax model was found to be preferable. BIV in baseline and EC_{50} were modeled with an exponential error model. No BIV could be estimated in the E_{max} parameter. The residual variability was modeled with an additive error model. By contrast to the results of the previously mentioned analysis,[51] the sex effect on the baseline QTc interval was significant (392 milliseconds in males and 400 in females). Other significant covariates affecting the baseline were congestive heart failure, paced-artificial pacemaker spike, and treatment with digoxin. Only the potassium level in serum had a statistically significant effect on EC_{50}. The estimated residual error SD was similar to that in the previously reviewed study[51]: 20.1 milliseconds, or 5% CV. Besides the above mentioned contribution of the suboptimal QT correction and the circadian rhythm, the estimated residual error may also include between-day variability of baseline within a patient (sort of between-occasion variability, BOV).

In a recent study by Bonate[12] PK-PD modeling of the QTcB interval prolongation caused by a noncardiovascular drug was performed. The following covariates were tested: day, period, sex, race, food, baseline serum potassium and calcium levels, and chest lead. Model terms were entered into the model in a linear manner, but the food effect was modeled as an exponential decline from maximal effect. A few models for the drug effect were tested including linear, power, and Emax models. The linear model was deemed the superior one. The data suggest that after controlling for sex, only the dose of medication was an important factor in the QTcB interval prolongation. Simulation was done to characterize the response surface as a function of each of the covariates identified from the population analysis.

All above reviewed studies used model-predicted concentrations as a driving force for the PD response, and this is a common practice in PK-PD modeling. Alternatively, when plasma sampling times are very close to ECG recordings one can use measured concentrations and skip the PK modeling step. There are, however, a few drawbacks in this approach. In particular, during the trial execution some actual sampling times may deviate substantially from scheduled ones. Also, the bioassay may accidentally generate outliers. Both factors will have a negative impact on the precision of PD parameter estimates.

Circadian Rhythm in QT and QTc

Both RR (or HR) and QT intervals are subject to within-day (circadian) variations.[55-59] Circadian rhythm is characteristic for QTc as well.[60-66] Figure 4 shows pooled, individually corrected (as described earlier) QT intervals before treatment vs the clock time in 26 unrelated healthy individuals from the previously presented data. The smoothing line indicates a circadian variation in QTc_I with the peak near 10 am.

In general, the statistical significance of the circadian rhythmicity can be documented by the cosinor analysis.[67,68] This method characterizes a rhythm by the parameters of a fitted cosine function or a multi-oscillator function that includes

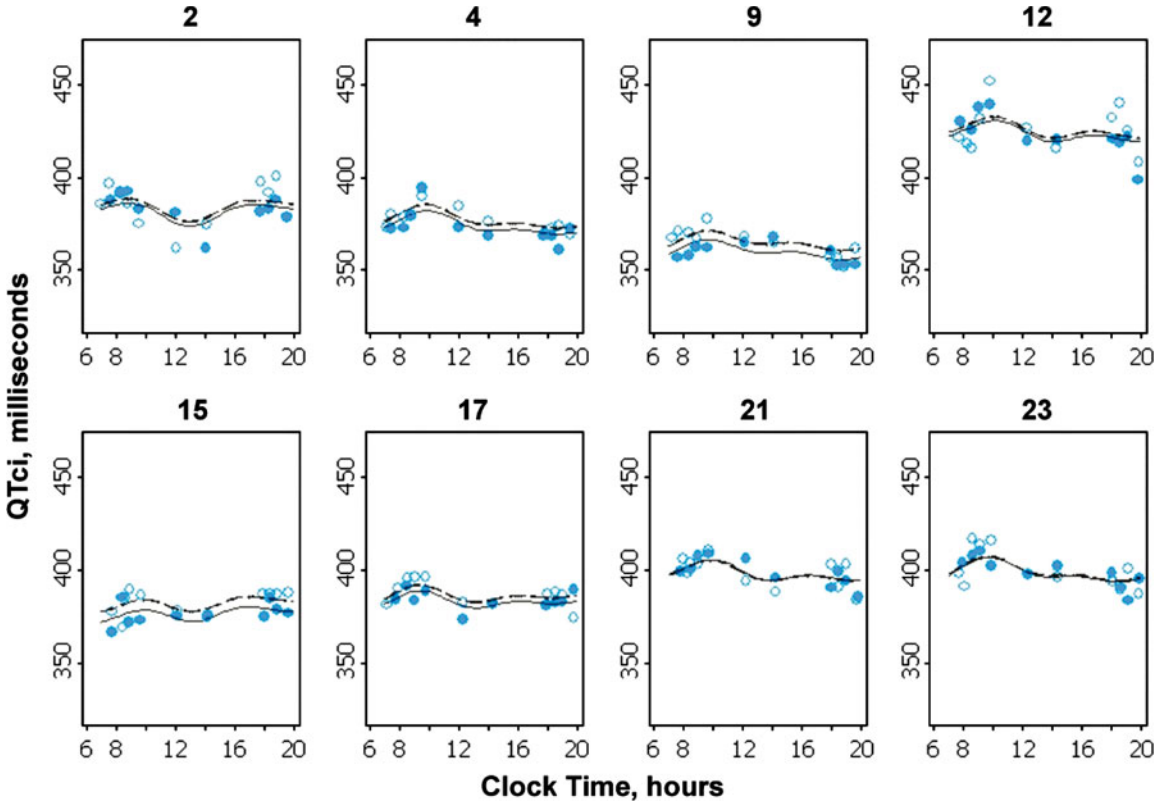

Figure 4. Individually corrected QT intervals (QTc_I) measured before treatment in 26 unrelated healthy individuals vs clock time (circles). The line is a loess smoother showing a circadian variation in QTc_I.

2 or more cosine functions with different periods. A circadian rhythm model for the QT interval (including the correction) may be represented as follows[31,69]:

$$QT_{ij} = QTcm_i \cdot RR_{ij}^{\alpha_i} \cdot (1 + CIRC_i) \cdot (1+\varepsilon_{ij}) \quad (12)$$

$QTcm_i$ is an individual mesor value of the corrected QT interval. The typical value will be further symbolized as QTcm. Other variables of the model (Equation 12) were introduced beforehand (Equation 5), except $CIRC_i$:

$$CIRC_i = A_{1,i}\cos[2\pi(t-\phi_{1,i})/24] + A_{2,i}\cos[2\pi(t-\phi_{2,i})/12] + A_{3,i}\cos[2\pi(t-\phi_{3,i})/6] \quad (13)$$

In case of 3 oscillators, the first period is 24 hours, the second 12 hours, and the third 6 hours. $A_{1,i}$, $A_{2,i}$, and $A_{3,i}$ are individual amplitudes; $\Phi_{1,i}$, $\Phi_{2,i}$, and $\Phi_{3,i}$ are acrophase parameters; t is the clock time ($t \in 0 \div 24$ hours). When t becomes equal to one of the Φs, the corresponding oscillator reaches its maximum. According to Equation 12, the amplitudes are fractions of the individual rhythm-adjusted mean baseline $QTcm_i$. The optimal number of the oscillators is selected based on the likelihood. Random BIV can be assumed for all parameters; however, the ability to estimate it is limited by the number of QT interval measurements available and their spread over the day. As it has been mentioned already, the precision of QT interval measurements is low, and a lot of observations are needed to extract a signal coming from the circadian rhythm. The estimation power is improved if all the data (not only pretreatment, but also on-treatment) are combined and a full model that includes also a drug effect module (see below) is fitted. In this case, not only BIV has to be taken into account, but also BOV at least in $QTcm_i$. This is necessary since in a typical cardiovascular safety study subjects are dosed at different days, which are often separated by long-lasting washout periods.

Examples of circadian variations in QTc_I calculated according to Equation 6 are presented in Figure 5. These values are generated based on the results of the full model fitted to the entire data set mentioned above, and lines are fitted curves consisting of 3 cosine functions with amplitude and acrophase parameters estimated via the Bayesian posterior procedure applied to the pretreatment data collected at 2 different study days. Occasions are marked by continuous and dashed lines, and close and open circles, respectively. In 2 subjects (nos. 21 and 23) profiles corresponding to occasions are not discernible, while in the others the difference is quite appreciable, although not as noticeable as BIV.Circadian rhythms in QTc_I can be a consequence of internal rhythmic processes and, at least partly, caused by food intakes that occur approximately at the same times of the day.

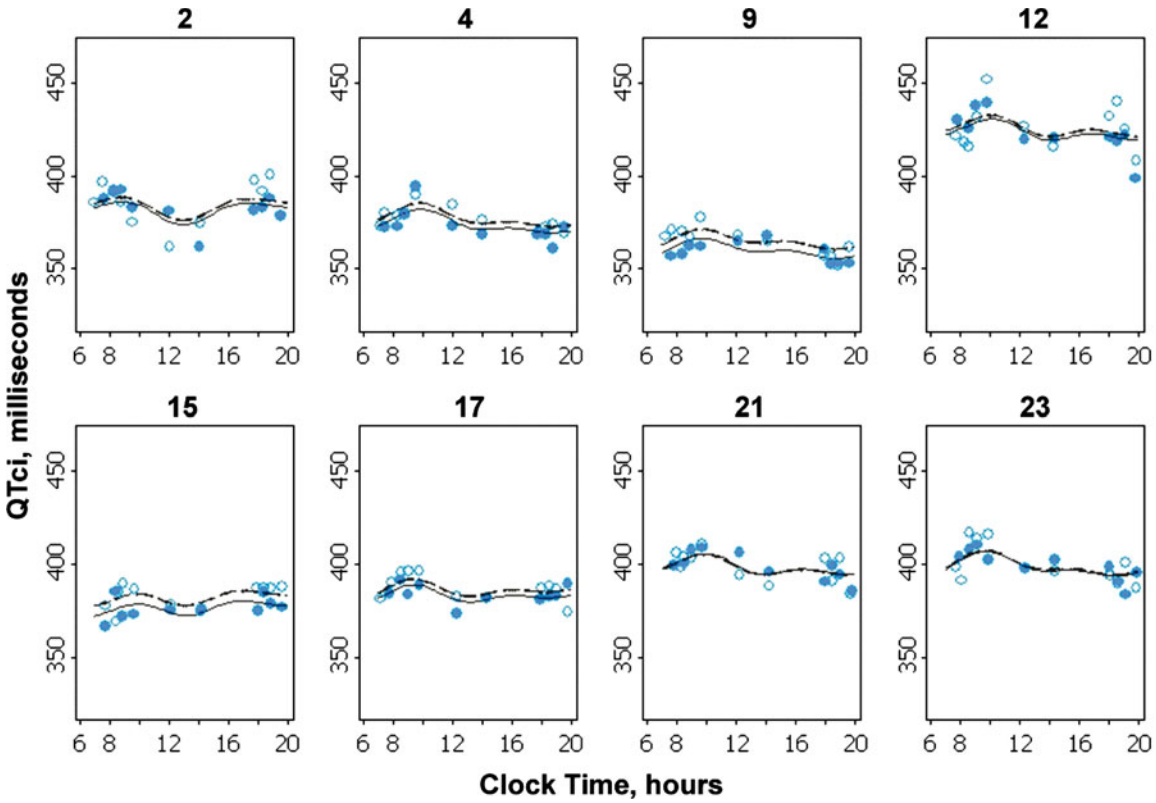

Figure 5. Examples of circadian variations in individually corrected QT intervals (QTc_I). Circles are QT/RRαi, and lines are fitted curves consisting of 3 cosine functions with amplitude and phase parameters estimated via the Bayesian posterior procedure. Occasions are set apart by using continuous and dashed lines and closed and open circles.

From these findings, it becomes evident that the definition of baseline needs modification when the quantitative assessment of the drug effect is concerned. In no case can the predose QTc interval or the mean pretreatment/placebo QTc interval serve as baseline. In the population modeling framework, baseline is an individual within-day QTc_I vs time profile that would be observed if the drug was not given. In order to evaluate baseline properly, the study has to be adequately designed and include at least 2 assessments per individual, one being after placebo.

Implementation of the Drug Effect

Thus, Equations 12 and 13 define an individual baseline profile. To implement a drug effect, a new term, E_i, meaning a fractional change in QTc_I caused by the drug, is added[31,69]:

$$QT_{ij} = QTcm_i \cdot RR_{ij}^{\alpha_i} \cdot (1 + CIRC_i + E_i) \cdot (1 + \varepsilon_{ji}) \quad (14)$$

where

$$E_i = f(C_i) \quad (15)$$

C_i is an individual plasma (or effect-compartment) concentration-time profile predicted by a separate population PK model to be developed before PD modeling. Individual parameters of such a model can be either estimated together with the parameters of the PD model (Equations 14 and 15) in one run, or separately. Both approaches have their pros and cons, which have been discussed elsewhere.[70]

The function *f* can be mechanism-based or just an empirical one depending on available information and on how factors other than the drug effect are described by the entire model. The impact of these factors should be partitioned well enough to allow the use of an appropriate drug effect model. As the goal of a cardiovascular safety study is to assess the QT interval prolongation potential of a drug candidate, one of the preferable PD submodels is the Hill function (sigmoid Emax model):

$$E_i = \frac{E_{\max,i} C_i^{H_i}}{C_{50,i}^{H_i} + C_i^{H_i}} \quad (16)$$

where $C_{50,i}$ is a concentration at which the effect is half of its maximum, $E_{max,i}$, and H_i is an exponent. The model represented by Equation 16 describes both activity (E_{max}) and potency (C_{50}); however it requires a substantial amount of information to estimate the parameters.

In most studies published so far, the linear model was used, and more complex PD models such as the (sigmoid) Emax

model were either not tested or did not provide better fit. The latter might be due to the use of an inadequate correction method, neglecting circadian rhythm, or ignoring BOV in baseline QTc, for example. The result was the increase of the residual error and the lack of the statistical power to estimate more realistic models with a maximum effect parameter. Another problem associated with the (sigmoid) Emax model estimation is that a drug may have low activity/potency (that is good for the compound, but not for modeling). In the case of C_{50} being beyond the normal therapeutic range, supratherapeutic doses may be needed.

A possible way to solve (some of) the problems of estimating drug effects on the QT interval is combining data of studies of various compounds with different activity/potency. In that way the overall power can be enhanced (more subjects included means more observations allowing better assessment of circadian rhythm parameters, correction exponent, and BOV) and more reliable estimates of PD model parameters can be achieved. In particular, a suggestion to include a positive control in the cardiovascular safety study design[9,71] has a potential to improve the parameter estimability. However, to apply the population PK-PD method in this case the bioassay of the active comparator should be available.

As it has been mentioned, C_i in Equation 16 may stand for plasma or effect-compartment concentration. The drug transport to cardiac tissues may account for the delay as indicated in some studies previously described.[42,47] However, the equilibration half-life was short and could be estimated mainly after intravenous administration.

Application of the PK-PD Model to Real Data of QT Interval Prolongation

In this section, the results of actual data modeling are briefly presented. The goal is to provide an illustrative example of how the PK-PD model for drug effects introduced in the previous sections works.

The data have been mentioned previously, and they will be described here in more detail. Two compounds were investigated: A and B. In study I, escalating doses of compound A were given orally to 24 healthy subjects. Each subject received 5 active doses and placebo. Twelve-lead ECG recordings were obtained frequently at each study day. A screening day and a pretreatment day preceded the treatment. An additional "end-of-trial" (posttreatment) day followed the treatment days. Plasma samples for the drug assay were collected at the times close to ECG recordings.

Compound B was investigated in studies II to IV in healthy subjects. All studies were single-dose. Study II was a cardiovascular safety study with frequent ECG recordings. Each individual (25 in total) received 2 active treatments and placebo in a random order at different days. Study III had a similar design; however, only 3 ECG recordings were obtained at each study day. The total number of subjects included was 20. In study IV, each of 24 subjects received either placebo or active treatment with ECGs frequently recorded.

Population PK models for both compounds were developed before PK-PD analysis using concentration-time data collected in studies I to IV. The structural part of the model was common (a 2-compartment linear model with first-order absorption), and individual Bayesian estimates of PK parameters were included in the NONMEM data sets prepared for PK-PD modeling to allow generation of plasma concentrations exactly at the times when ECG was recorded. Data sets of all 4 studies were combined before PK-PD modeling.

Measured RR intervals were included in the data set, and no separate PK-PD modeling for RR intervals was done. This method might introduce some additional uncertainty in the QT interval modeling results; however, the precision of the RR interval measurements are much higher compared with the QT interval since the former is the distance between 2 well-defined peaks (Figure 1). The impact of using measured RR intervals instead of model-predicted ones still remains to be explored. Nevertheless, variability in RR intervals caused, for instance, by the circadian rhythm and the potential drug effect is adequately captured when measured intervals are used in PK-PD modeling.

Combining several studies increases the robustness of estimates of non-drug-related parameters that can be called "system parameters": QTcm, α, amplitudes, and acrophases. Also, the number of cosine functions in the circadian rhythm submodel can be unequivocally identified. In our case, models with 2 and 3 cosine functions were compared. The inclusion of the third cosine with the period of 6 hours resulted in a highly significant improvement of the fit (the NONMEM objective function value decreased by almost 50). Table 1 gives the summary of estimates of the system parameters. Figure 6 shows some goodness-of-fit plots.

The mesor baseline parameter, QTcm, differs between males and females and is in line with observations of other researchers.[12,51,52] While QTcm is subject to random BIV and BOV, no study effect was seen. The correction exponent α varied from individual to individual, but no within-subject variability was observed; this result is in accordance with the findings of Batchvarov et al.[26]

The drug effect submodel had initially 2 pairs of E_{max} and C_{50} to account for the potential disparity in the activity and potency between the 2 drugs. No difference in the Hill parameter was assumed. Finally, it turned out that E_{max} for compound B was small, and its statistical significance could not be proven. Thus, only E_{max} and C_{50} related to compound

Table 1. Estimates of the System Parameters Describing the QT Interval Correction and the Circadian Rhythm Obtained Using the First-Order Conditional Estimation Method of NONMEM*

Parameter (units)	Estimate for a Typical Individual	Between-Individual Variability (%CV)	Between-Occasion Variability (%CV)
QTcm (milliseconds)	375 (males) 389 (females)	4.1	1.2
Correction exponent α	0.22	23	NE
24-hour cycle amplitude	0.018	NE	NE
24-hour cycle acrophase	13	10.5	NT
12-hour cycle amplitude	0.012	39	NT
12-hour cycle acrophase	8.2	12	NT
6-hour cycle amplitude	0.0055	NE	NT
6-hour cycle acrophase	3.6	26	NT

*CV indicates coefficient of variation; NE, not estimable; and NT, not tested.

A were estimated in the final model, and compound B had no effect. Also an attempt has been made to include the effect compartment in the PK-PD model; however, no improvement of the fit was obtained.

Estimated residual error CV was lower compared with the estimates reported by the authors who performed population PK-PD modeling of QT interval data: 2.8% vs 5%.[51,52] The reduction of the residual error was evidently the result of inclusion of the circadian rhythm and BOV in the model, and also of the individualized QT interval correction.

For the graphical presentation of the concentration-effect relationship, the observations were corrected to eliminate variability caused by both RR intervals and the circadian rhythm. Therefore the correction was slightly different from that by Equation 6. It was based on model Equation 14, and is shown below:

$$QTcl^* = QT_i/RR_{ij}^{\alpha_i} - QTcm_i \cdot CIRC_i \qquad (17)$$

Figure 7 shows how QTc_I* derived via Equation 17 depend on the plasma concentration. Figure 8 gives examples of individual fits for subjects, in which sufficiently high plasma concentrations were achieved and full effect could be observed. The estimates of drug-effect-related parameters are summarized in Table 2.

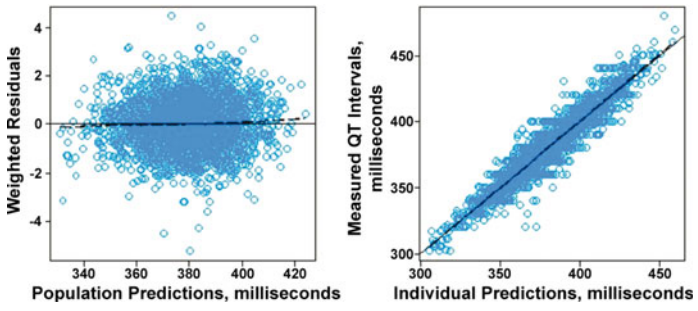

Figure 6. Goodness-of-fit plots. Dashed lines are loess smoothers.

For this particular analysis, compound A can be considered as a positive control for compound B, which demonstrated a negligible effect. No sex difference in the E_{max} parameter was found; however, due to higher QTcm in females (Table 1), the maximum absolute drug effect for a typical female and male is different: 414 and 399 milliseconds, respectively, meaning that females were at slightly higher risk of prolonged QTc intervals. There was also a small difference in terms of changes from baseline: 25 and 24 milliseconds for a typical female and male, respectively, although this difference was not statistically significant.

The ICH Preliminary Concept Paper[9] provides the following limits to be taken into account when analyzing QT/QTc interval prolongation data:

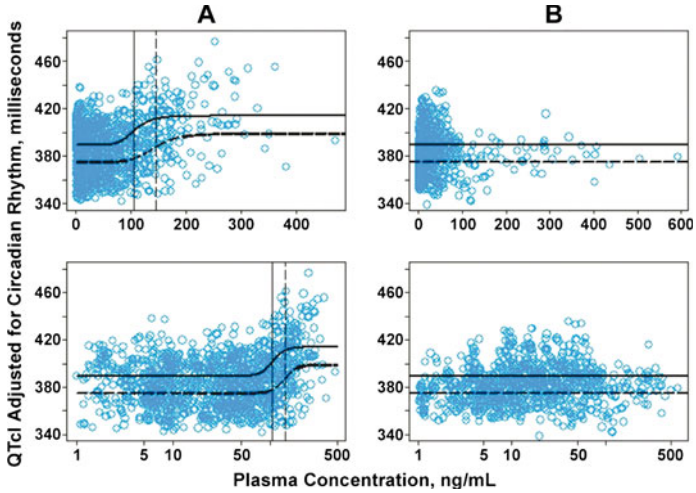

Figure 7. QT intervals individually corrected through Equation 16 (QTc_I*) vs plasma concentrations of compound A and B (the upper row: linear plots; the bottom row: semilogarithmic plots). Bold lines show typical model-predicted profiles for males (dashed lines) and females (continuous lines). Vertical lines denote C_{50} values for males and females (compound A only; dashed and continuous lines, respectively).

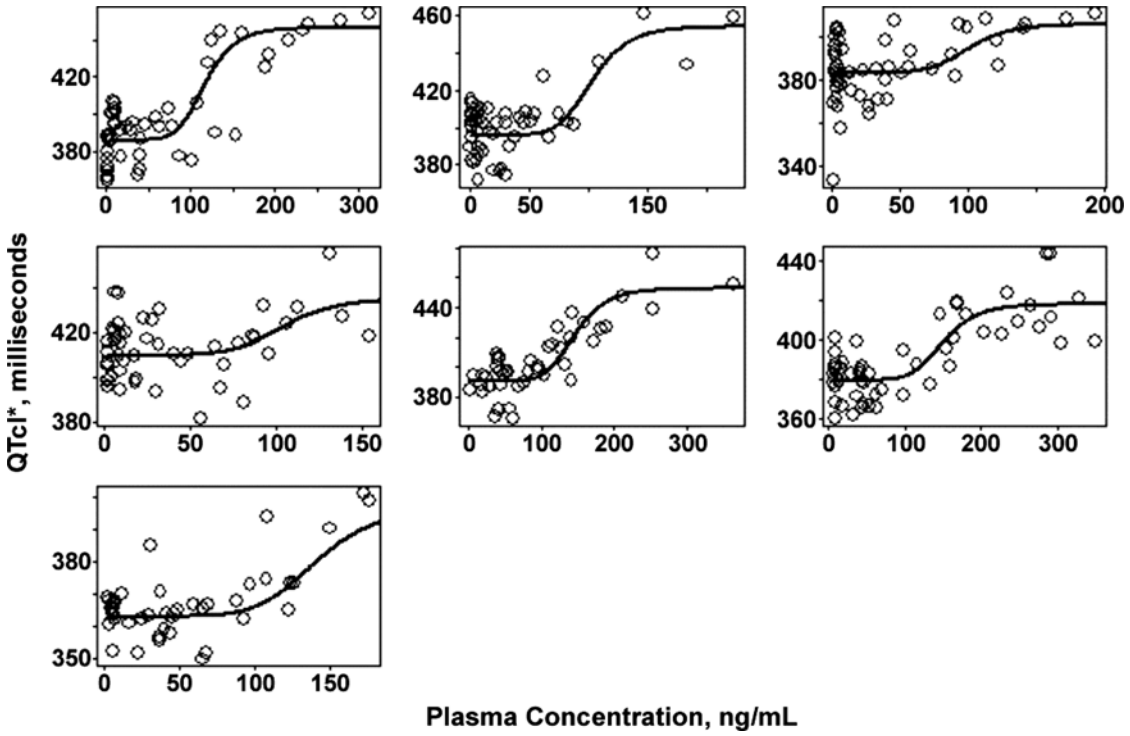

Figure 8. Examples of individual fits.

Absolute QTc interval prolongation (milliseconds):

- QTc interval > 450
- QTc interval > 480
- QTc interval > 500

Change from baseline in QTc interval (milliseconds):

- QTc interval increases from baseline ≥30
- QTc interval increases from baseline ≥60

These limits should be applied to individual estimates, not to typical values that do not say anything about individual safety. BIV in E_{max} is high (55%, Table 2), and there may be subjects with the maximum QTc_I prolongation substantially exceeding the typical value. This is illustrated by Figure 9, which shows histograms of individual maximal QTc_I derived via Equation 6, and changes from baseline (ΔQTc_I) calculated on the basis of Bayesian parameter estimates. Note that variability coming from the circadian rhythm is preserved in this computation. Also, results of simulation based on the model (1000 individuals, equal proportion of males and females) are presented in the same figure in the form of empirical densities. In Figure 9, the upper 2 panels present subjects participating in the study of compound A. The bottom panels show histograms of maximal QTc_I and ΔQTc_I calculated for subjects receiving compound B; simulated densities thus do not include any drug effect. Circadian variability is nevertheless taken into account, and it results in ΔQTc_I shifted toward positive values. They, however, do not exceed 20 milliseconds. Figure 9 clearly demonstrates that compound A may cause the QTc_I interval prolongation beyond the above-mentioned limits in some subjects, and the fraction of subjects is especially high in case of ΔQTc_I (Table 3).

Table 2. Estimates of the Drug A Effect Submodel Parameters Obtained Using the First-Order Conditional Estimation Method of NONMEM*

Parameter (units)	Estimate for a Typical Individual	Between-Individual Variability (%CV)	Between-Occasion Variability (%CV)
E_{max}	0.064	55	NE
C_{50} (ng/mL)	140	12	18
C_{50} female/male ratio	0.73	-	-
H	6.8	NE	NE

*CV indicates coefficient of variation; E_{max}, maximum drug effect; NE, not estimable; C_{50}, concentration at which the effect is half of the maximum; and H, sigmoidicity parameter.

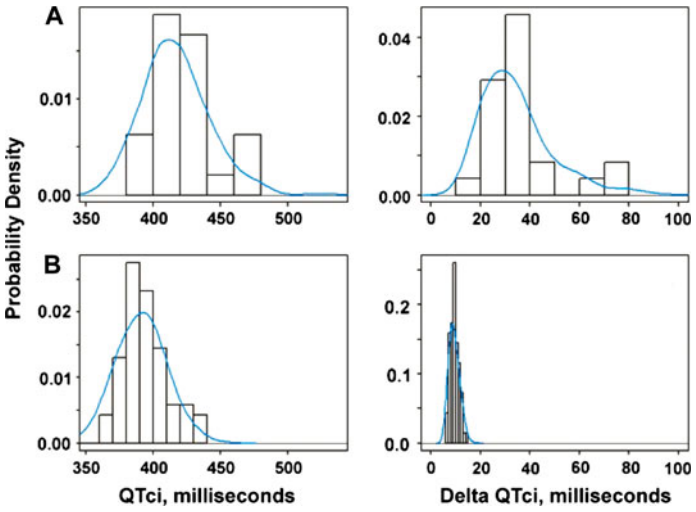

Figure 9. Histograms summarizing the distribution of individual (Bayesian) model-predicted maximum QTc_I intervals and ΔQTc_I in subjects who participated in study I (compound A) and studies II-IV (compound B). Smoothing lines (loess smoother) are empirical densities of simulated QTc_I intervals and ΔQTc_I from 1000 simulated individuals.

The preceding considerations concern the maximum QTc_I response that can only be observed at the plasma concentrations above 200 ng/mL (see Figure 7). The steepness of QTc_I-C relationship is quite high (Hill parameter H is ~7, Table 2), and compound A is safe both in males and females unless plasma concentration exceeds 70 ng/mL. Note that due to sex disparities in the potency (C_{50}), safety margins are narrower in females compared with males (Figure 7). While on average there is almost no QTc_I prolongation in males at 100 ng/mL, this level may produce ~50% of maximum effect in females.

PK-PD Modeling and the Standard Biostatistical Analysis of Cardiovascular Safety Data

The ICH Preliminary Concept Paper[9] provides an overview of methods that are recommended to assess the cardiovascular safety of drugs. According to this document, the QT/QTc interval data should be presented both as analyses of central tendency (eg, means, medians) and categorical analyses.

The effect of an investigational drug on the QT/QTc interval is most commonly analyzed using the largest time-matched mean difference between the drug and placebo (baseline-subtracted) over the collection period (eg, hourly, weekly, monthly). Additional approaches to the assessment of central tendency could include the analysis of time-averaged QT/QTc intervals or the analysis of changes occurring at the plasma concentration peak (C_{max}) for each individual. This approach (herein referred to as standard) has an advantage of not using sophisticated statistical tools and specialized software. However, the traditional evaluation has many deficiencies, some of which are summarized below:

1. It provides no quantitative information on the QT prolongation triggered by a drug either in terms of activity or potency. Thus the standard approach may have its value for regulatory purposes but is not sufficient for drug development in which the usual goal is estimating activity and potency of a compound, and evaluating safety margins.
2. Moreover, it seems that most complications and fatal events potentially related to QT/QTc interval prolongation occurred either after taking supratherapeutic doses of drugs or as a consequence of co-administration of potent metabolic inhibitors. By contrast to the standard approach that only assesses the extent of prolongation at the peak of actual plasma concentration, the model-based method enables the estimation of the ultimate QT prolongation potential (ie, E_{max}) of a drug and the testing (through simulation) of various scenarios, which cannot be investigated in clinical studies with healthy subjects.
3. Time-averaging substantially reduces the sensitivity of the test.
4. Due to BIV of PK profiles the time to C_{max} may differ substantially between individuals, and the sampling times selected based on mean profiles can miss the true C_{max} for substantial proportion of subjects resulting in underestimating of the actual magnitude of QT/QTc prolongation. This problem is especially important in case of immediate-release oral formulations with sharp plasma concentration peaks.

Table 3. Percentage of Subjects With QTc_I and ΔQTc_I Exceeding Thresholds Recommended in the ICH Preliminary Concept Paper*

Threshold	Actual Data	Simulated Data (n = 1000, 50/50 males and females)
$QTc_I > 450$	12.5	9.7
$QTc_I > 480$	0	1.3
$QTc_I > 500$	0	0.4
$\Delta QTc_I \geq 30$	67	56.5
$\Delta QTc_I \geq 60$	12.5	7.1

*ICH Preliminary Concept Paper[9]

5. Baseline subtraction inevitably leads to at least doubling the variance of the difference compared with that of original values and reduces the power of any test for the drug effect.

Categorical analyses of QT/QTc interval data as suggested by the ICH Preliminary Concept Paper are based on the number and percentage of patients meeting or exceeding some predefined upper limit value.[9] Clinically noteworthy QT/QTc interval signals might be defined in terms of absolute QT/QTc intervals or changes from baseline. Absolute interval signals are QT/QTc interval readings in excess of some specified threshold value. Separate analyses should be provided for patients with normal and elevated baseline QT/QTc intervals. Categorical analyses are most informative when it is possible to compare the rate of suprathreshold readings in the treatment and control groups.[9]

Thus, the categorical analysis is bound to raw measurements to an even bigger extent than the analysis based on the central tendency. Taking into account the fact that the random variability of QT measurements is high as shown previously, and outlying measurements are quite common, the categorical analysis is associated with a high chance of false-positive or false-negative outcome, especially if the number of subjects included in a "thorough QT/QTc study" is relatively low.

More advanced metrics were suggested and compared with the standard ones through clinical trial simulation.[72,73] It has been shown that the most sensitive metric is the area under QTc-time curve with baseline QTc as a covariate.

By contrast to the standard approach based on raw measurements, population modeling (when correctly applied) not only gives answers to the question of safety, but also provides quantitative information on the drug activity and potency. The inference with respect to the central tendency is based on well-grounded criteria such as the likelihood ratio test and parametric and nonparametric confidence intervals. The model-based approach is by definition much more robust with respect to outliers compared with the standard methods. Through simulation the risks of exceeding safety thresholds in the population (an analog of the categorical analysis) can be easily assessed. Bonate[12] also showed how the false-positive rate in a study can be determined through Monte Carlo simulation.

An essential condition for activity/potency estimation via population PK-PD modeling is using sufficiently high doses to ensure that the concentration achieved allows estimating a maximum response. On the other hand, if maximum concentration is not high enough, simpler PD models can be used instead of the (sigmoidal) Emax model. Of importance, however, is that any model having no maximum effect parameter can only be employed to establish safety margins of the drug and is only applicable within the concentration range studied. No extrapolations beyond this range can be made as this will inevitably lead to the overestimation of the cardiovascular risk. In fact, if a particular study revealed the fact of QT/QTc prolongation but failed in the estimation of the maximum response, another study would have to be conducted with increased doses or with the use of potent metabolic inhibitors as recommended in the ICH Preliminary Concept Paper.[9] It is expedient to initialize such a study after establishing the dose range to be used in clinical practice (thus, after phase 2B).

Population modeling allows efficient combining of 2 or more studies thereby increasing the overall power. Studies to be combined may have completely different designs; in particular, safety studies in which subjects are frequently assessed can be combined with phase 2 studies with sparse blood sampling and ECG recording. In this way the cardiovascular safety in the target patient population can be effectively assessed. Separate analysis of sparse PK-PD data without supportive information that is only available in well-controlled phase 1 studies is hardly feasible.

The ICH Preliminary Concept Paper suggests using a positive control (a drug known to prolong the QT/QTc interval) "to establish assay sensitivity."[9] The usefulness of the positive control may be substantially increased if the design of a thorough QT/QTc study includes plasma concentration assay of the active comparator together with the drug of interest followed by an extensive PK-PD modeling. Such an approach will increase the trustworthiness of the study results.

CONCLUSION

While the degree of QT interval prolongation is recognized as an imperfect biomarker for the proarrhythmic risk, there is at least a qualitative relationship between QT prolongation and the risk of TdP, especially for drugs that cause substantial prolongation of the QT/QTc interval. In this review, factors affecting the QT interval and the methods that are currently in use in the analysis of drug effects on the QT interval duration were overviewed with the emphasis on population PK-PD modeling.

Due to multiple sources of variability and potentially low precision of QT measurements resulting in a low signal-to-noise ratio, the standard approach based on the raw observations and formal statistics may lead to false-positive or false-negative conclusions, especially when the individual risk is concerned. Population PK-PD modeling offers a potent tool to split the overall variability into components and to estimate them. In the literature, however, there are only a few publications in which population PK-PD modeling is applied to QT interval prolongation data.

A comprehensive PK-PD model is introduced that incorporates an individualized QT interval correction, a circadian

rhythm in baseline QTc_I, and a drug effect. Using this model may solve at least some of the problems inherent in the standard analysis methods and also provide a basis for simulation that may help in designing better cardiovascular safety trials.

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